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EXAMINER	
ROBINSON, HOPE A	

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1653	

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Please find below and/or attached an Office communication concerning this application or proceeding.

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

PAPER NO: 09142004

Examiner: Hope Robinson

Art Unit: 1653

Application Serial Number: 09/180,340

Filing Date: August 20, 1999

Appellant(s): Nancy Ho

Zheng-Dao Chen

David L. Provence

For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed on July 1, 2004.

EXAMINER'S ANSWER

(1) Real Party in Interest

This is in response to appellant's brief on appeal filed July 1, 2004. A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences, which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statements of the status of amendments after final rejection contained in the brief is correct. As the appellant filed an amendment concurrently with the Brief an Advisory Action has been issued (mailed on September 8, 2004).

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 14-16, 18, 30 and 32-33 stand or fall together; claims 28 and 34 stand or fall together and claims 17 and 29 stand or fall together. However, the appellant's brief does not provide reasons as set forth in 37

CFR 1.192(c)(7) and (c)(8). It is noted that the appellant states that reasons would be provided in the argument section of the brief, however, this was not addressed, the arguments discuss the references used in the rejections of record and points out differences, not how the claims are separately patentable.

(8) Claims Appealed

Claims on appeal have been presented correctly.

(9) Prior Art of Record

Ho et al in view of Lopes et al. and Ho et al. in view of Hallborn et al. cited art, has been applied in the grounds of rejection under 35 U.S.C. 103.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

35 U.S.C. 103 reads as follows:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejections have been amended in view of the amendment filed concurrently with the Brief, which cancelled several rejected claims.

Issue A:

Claims 14-18, 28-30 and 32-34 stand rejected under 35 U.S.C. 103(a) as obvious over Ho et al. (WO 95/13362, May 18, 1995) in view of Lopes et al. (Yeast, vol. 12, no. 5, pages 467-477, April 1996).

Ho et al. teach recombinant yeasts containing genes encoding xylose reductase, xylitol dehydrogenase and xylulokinase, DNA molecules, plasmid vectors and methods useful for producing said yeasts which are capable of fermenting xylose to ethanol and glucose to ethanol. Ho et al. teach direct amplification of the intact xylitol dehydrogenase gene and the promoter less xylitol dehydrogenase from *Pichia stipitis* chromosomal DNA (see Figure 10 and page 10). Ho et al. disclose that suitable sources of xylitol dehydrogenase and xylose reductase genes include xylose-utilizing yeasts such as *Candida shehatae*, *Pichia stipitis*, *Pachysolen tannophilus* and suitable sources of xylulokinase genes include the above yeasts as well as xylose non-utilizing yeasts such as those from the genus *Saccharomyces cerevisiae*, *Schizosaccharomyces*

pombe and bacteria such as *Eschericia coli* etc. (see page 13). Additionally, Ho et al. teach selection markers (pages 15-16) and specific DNA fragments that serve as replicons and selection markers that enable the plasmid to be replicated autonomously in *S. cerevisiae*. In-so-far-as Ho et al. does not explicitly teach the integration at multiple sites, Lopes et al. teach numerous plasmids containing various genes integrated into a RNA gene of *S. cerevisiae.* Multiple copies of the plasmid were successfully integrated into the genome (over 140 copies), which are stably maintained in non-selective medium for generations over long periods of time (see abstract and pages 467-475). Further, the plasmids contained a Leu2d selection marker and various cloned genes for stability and expression studies. Yeast transformants were selected by plating on agar plates containing yeast nitrogen base (without amino acids), glucose and histidine. The same medium was used for growing the transformants in liquid culture (see page 468 and Figure 1 and see for example claim 14).

Therefore, it would have been obvious to one of ordinary skill in the art to arrive at the claimed invention as a whole by combining the teachings of Ho et al. and Lopes et al. because Ho et al. teach the simultaneous fermentation of xylose and glucose into ethanol from the yeast *S. cerevisiae,* as ethanol is said to be an ideal liquid fuel for automobiles and Lopes et al. teach a method of making transformants stably maintained in non-selective medium for multiple generations over long periods of time. One of ordinary skill in the art would be motivated to combine the teachings of both references because the method taught by Ho et al. introduces DNA into the same yeast

taught by Lopes et al. Thus, the claimed invention was obvious to make and use at the time the invention was made and was *prima facie* obvious.

(11) Arguments:

Response to Arguments for Issue A

Appellants on page 5 (first paragraph) cites *In re Hoch* and state that" [W]here a reference is relied on to support a rejection, whether or not in a minor capacity, that reference should be positively included in the statement of rejection. Firstly, the fact pattern of *In re Hoch* does not match the facts of the instant case, therefore, this argument is not persuasive. Secondly, the cited art of record by Lopes et al. has an embodiment by Lopes et al. of earlier results. The cited reference discloses "We have recently developed a novel type of vector called pMIRY2 (for Multiple Integration in the Ribosomal DNA of Yeast) that integrates into the ribosomal DNA locus of *Saccharomyces cerevisiae* in up to 140 copies which are stably maintained over long periods of growth under non-selective conditions". Lopes et al. disclose their findings, which is relevant and does not require the presentation of the earlier reference as held in *In re Hoch*.

It is further stated on pages 5-6 that the cited prior art does not teach or suggest the use of a replicative and integrative plasmid comprising an autonomous replicating sequence and exogenous DNA in a cell to result in progeny of the cell having multiple integrated copies of the exogenous DNA. This argument is not persuasive because on page 16 of the Ho et al. reference, it is disclosed that specific DNA fragments serve as

replicons and selection markers which enables the plasmid to be replicated autonomously in *S. cerevisiae* and closely related species (see lines 26-29). It is further stated that plasmids such as pLNH33 and pLNH21 are used to transform *S. cerevisiae* (see page 17, lines 5-6 of Ho et al. reference). Although the Ho et al. reference does not explicitly teach integration, the reference teaches plasmids which are disclosed in the instant specification as replicative and integrative. See page 18, lines 31-32 where it is disclosed that pLNH-ST is both a replicative vector and an integrative vector (see also page 14, lines 1-3, where it is disclosed that pLNH 33 is a replicative plasmid, in the instant specification). Additionally, the reference disclose fermenting xylose with recombinant yeast SC (pLNH21), *S. cerevisiae* containing introduced XR, XD and XK genes (see page 9). The Lopes et al. reference teaches introduction of homologous genes by means of the vector (integrative), see for example pages 52 and 472 of the reference.

The appellants also state that there is no motivation to combine the cited documents (see page 7 of the Brief), however, this argument is not persuasive. Note that the Ho et al. reference and the Lopes et al. reference both teach yeast from *Saccharomyces cerevisiae* and the introduction of genes by means of a vector to produce stable transformants. Lopes et al. teach a replicative and integrative plasmid vector. Additionally, the appellants on the bottom of page 7 to the beginning of page 8 cite the previous office action, indicating that the evidence provided indicate that Ho et al. and Lopes et al. could be combined. *In re Mills* is also cited and appellants state that the mere fact that the references can be combined or modified does not render the

resultant combination obvious. This argument and the arguments presented on pages 8-9 are not persuasive in view of the teaching of the references, because the combined teaching of the references provides a vector that permits autonomous replication, has exogenous DNA and a flanking sequence, has multiple integration in rDNA of yeast up to 140 copies and is stably maintained over time.

On pages 10-11, the appellants state that the combination of Ho et al. with Lopes et al. could not produce the claimed invention because Lopes et al. indicate that size is crucial, thus, the DNA to be inserted includes genes encoding XR, XD and XK in the Ho et al. reference. Note that claims 14-16, 18, 28, 30 and 34 do not recite the genes encoding XR, XD and XK. It is noted that claim 17 recites genes encoding XR, XD and XK, however, note that the first selection marker could be all three or any one of the three based on the present claim language. Note also that Ho et al. disclose recombinant yeasts containing genes encoding XR, XD and XK, thus the appellant's statement that the combination of the references might result in reduced mitotitic stability is not persuasive.

Issue B:

Claims 28-29 and 34 stand rejected under 35 U.S.C. 103(a) as obvious over Ho et al. (WO 95/13362, May 18, 1995) in view of Hallborn et al. (CA 2090122, October 17, 1991).

Ho et al. teach recombinant yeasts containing genes encoding xylose reductase, xylitol dehydrogenase and xylulokinase, DNA molecules, plasmid vectors and methods

useful for producing said yeasts which are capable of fermenting xylose to ethanol and glucose to ethanol. Ho et al. teach direct amplification of the intact xylitol dehydrogenase gene and the promoter less xylitol dehydrogenase from *Pichia stipitis* chromosomal DNA (see Figure 10 and page 10). Ho et al. disclose that suitable sources of xylitol dehydrogenase and xylose reductase genes include xylose-utilizing yeasts such as *Candida shehatae*, *Pichia stipitis*, *Pachysolen tannophilus* and suitable sources of xylulokinase genes include the above yeasts as well as xylose non-utilizing yeasts such as those from the genus *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe* and bacteria such as *Eschericia coli* etc. (see page 13). Additionally, Ho et al. teach selection markers (pages 15-16) and specific DNA fragments that serve as replicons and selection markers that enable the plasmid to be replicated autonomously in *S. cerevisiae*. In-so-far-as Ho et al. does not explicitly teach the integration at multiple sites, Hallborn et al. teach recombinant yeasts that ferments xylose to ethanol, having genes integrated (multiple copies) into the yeast chromosome. The genes taught by Hallborn et al. encode xylose reductase and xylitol dehydrogenase. Hallborn et al. also teach yeast from *Saccharomyces* and a method of transforming cells with integrative plasmids. Additionally, the vector taught by Hallborn et al. autonomously replicates multiple copy plasmids (see pages 1-9).

Therefore, it would have been obvious to one of ordinary skill in the art to arrive at the claimed invention as a whole because Ho et al. and Hallborn et al. teach the fermentation of sugars to ethanol (i.e. xylose and glucose) using the same yeast strain. One of skill in the art would reasonable expect successful results by combining the two

references because Hallborn et al. teach integrative plasmids and an autonomously replicating plasmid suitable for carrying out transformation stably. Moreover, one of skill in the art would be motivated to combine the teachings of the references because Ho et al. disclose that ethanol is an ideal liquid fuel for automobiles and Hallborn et al. disclose a method to perform stable transformations over time. Therefore, the claimed invention was *prima facie* obvious.

Response to Arguments for Issue B

On page 12 (in the last paragraph of the Brief), appellants state that Ho et al. disclose the use of plasmids containing a 2 μm origin of replication and it is concluded that this is not an autonomous replicating sequence. On page 16 of the Ho et al. reference, it is disclosed that specific DNA fragments serve as replicons and selection markers which enables the plasmid to be replicated autonomously in *S. cerevisiae* and closely related species (see lines 26-29). It is further stated that plasmids such as pLNH33 and pLNH21 are used to transform *S. cerevisiae* (see page 17, lines 5-6 of Ho et al. reference). Although the Ho et al. reference does not explicitly teach integration, the reference teaches plasmids which are disclosed in the instant specification as replicative and integrative. See page 18, lines 31-32 where it is disclosed that pLNH-ST is both a replicative vector and an integrative vector (see also page 14, lines 1-3, where it is disclosed that pLNH 33 is a replicative plasmid, in the instant specification). Additionally, the reference disclose fermenting xylose with recombinant yeast SC (pLNH21), *S. cerevisiae* containing introduced XR, XD and XK genes (see page 9).

Appellants on page 13 (at the second paragraph from the bottom of the page) state that some vectors taught by Hallborn et al. include exogenous DNA and are capable of replicating autonomously, however, do not teach flanking DNA that is homologous to a reiterated DNA sequence of a target yeast cell. Therefore, the appellants conclude that the combination of the vectors of Ho et al. with the type of vectors disclosed by Hallborn et al. would result in a vector containing exogenous DNA and an origin of replication that permits autonomous replication, but the exogenous DNA would not be flanked by a DNA flanking sequence which is homologous to a reiterated ribosomal DNA sequence of a target yeast cell. In addition, the appellants conclude on page 14 (in the first paragraph) that the combination of the vectors of Ho et al. and Hallborn et al. would result in a vector containing a 2 μm origin of replication, exogenous DNA, and flanking DNA that is homologous to a reiterated ribosomal DNA sequence of a target yeast cell, but would not contain functional yeast autonomous replicating sequence (claims 28, 29 and 34). The conclusions made by the appellants on pages 13 and 14 appear to be contradictory. For example, the appellant's on page 13 indicate that the combined teaching of the references results in a vector that permits autonomous replication, however on page 14 it is said that the combined teaching of the references would not result in a functional yeast autonomous replicating sequence. Note also that on page 13 it is stated that the exogenous DNA would not be flanked, however, on page 14 it is stated that the exogenous DNA is flanked by a homologous reiterated ribosomal DNA sequence of a target yeast cell.

Moreover, Figure 2 of the Ho et al. reference disclose nucleotide sequences and deduced amino acid sequences of the yeast xylulokinase gene including 5' and 3' flanking sequences. In addition, page 7 of the Hallborn et al. reference disclose flanking by ribosomal sequences (see lines 27-28) and Hallborn et al. by producing multiple copies of the same DNA to be integrated renders the claimed invention as obvious. Therefore, the combined teaching of Ho et al. and Hallborn et al. provides vectors that contain exogenous DNA that is flanked by 5' and 3' DNA sequences, that permits autonomous replication which is homologous to a reiterated rDNA sequence of a target yeast. In view of the inconsistency in the appellant's statements regarding the combined teaching of the references the comments made in the last two paragraphs on page 14 and the first two paragraphs on page 15 are not persuasive. Appellants have stated on the record what the combined teaching of the references result in and to later recant such statements on another page is not persuasive.

The last paragraph on page 15 and the paragraphs on page 16 indicate that there is no motivation to combine or modify the cited documents, however, this argument is not persuasive in view of the following statements made by the appellants. The appellants have stated on pages 13-14 that "the vectors of Ho et al. with the type of vectors disclosed by Hallborn et al. would result in a vector containing exogenous DNA and an origin of replication that permits autonomous replication, but the exogenous DNA would not be flanked by a DNA flanking sequence which is homologous to a reiterated ribosomal DNA sequence of a target yeast cell" and " the combination of the vectors of Ho et al. and Hallborn et al. would result in a vector containing a 2 μm origin

of replication, exogenous DNA, and flanking DNA that is homologous to a reiterated ribosomal DNA sequence of a target yeast cell, but would not contain functional yeast autonomous replicating sequence (claims 28, 29 and 34), emphasis added. All the limitations of the claims are taught by the combined teaching of the references for the reasons stated above in the rejection of record and as the appellant's concluded in enumerating the combined teaching of the references. Note also that on page 16, lines 6-7 the appellants state that "[T]his statement may show that the two documents could be combined", indicating that evidence has been provided to demonstrate the commonality between the two references such that the teaching could be combined. Therefore one of ordinary skill in the art would be motivated to combine the references as their teaching result in the claimed vector.

Appellants state that there is no reasonable expectation of success (see the bottom of page 16 and all of page 17). This statement is not persuasive. The combined teachings of the references results in the plasmid vectors recited in claims 28, 29 and 34 as set forth in the above rejection and in reviewing the conclusion statements made by the appellants. The appellants state that the combined teaching of the reference "results in a vector that..." thus the expectation of success is not an issue because of the resulting effect. On page 17 (in the second paragraph), the appellants state that "Hallborn et al. teach non-replicative integrative fragments and do not teach or suggest integrative plasmids. Briefly, Hallborn et al. teach the construction of a plasmid carrying an exogenous DNA that is to be integrated". Clearly, the statements made by the

appellants are inconsistent. Does the appellant's statements of "a brief teaching by Hallborn et al." qualify as a suggestion which meets the standard of 35 U.S.C. 103?

The appellant's arguments have been considered and addressed, however, are not persuasive because of the inconsistency in statements made and the facts presented in the references, which render obvious the claimed invention.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Examiner Hope Robinson

Conferees:

JON WEBER
SUPERVISORY PATENT EXAMINER

September 14, 2004

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